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Novel Missense Mutation in the Cyclic Nucleotide-Binding Domain of *HERG* Causes Long QT Syndrome

Carol Ann Satler, Edward P. Walsh, Mark R. Vesely, Mark H. Plummer, Geoffrey S. Ginsburg, and Howard J. Jacob

Department of Cardiology, Children's Hospital (C.A.S., E.P.W., M.R.V., M.H.P., G.S.G.), Boston, Cardiovascular Division, Beth Israel Hospital (G.S.G.), Boston, Harvard Medical School (C.A.S., E.P.W., M.R.V., M.H.P., G.S.G.) Boston, Massachusetts; and Department of Physiology, Medical College of Wisconsin (H.J.J.), Milwaukee, Wisconsin

Autosomal-dominant long QT syndrome (LQT) is an inherited disorder, predisposing affected individuals to sudden death from tachyarrhythmias. To identify the gene(s) responsible for LQT, we identified and characterized an LQT family consisting of 48 individuals. DNA was screened with 150 microsatellite polymorphic markers encompassing approximately 70% of the genome. We found evidence for linkage of the LQT phenotype to chromosome 7(q35–36). Marker *D7S636* yielded a maximum lod score of 6.93 at a recombination fraction (θ) of 0.00. Haplotype analysis further localized the LQT gene within a 6.2-cM interval. *HERG* encodes a potassium channel which has been mapped to this region. Single-strand conformational polymorphism analyses demonstrated aberrant bands that were unique to all affected individuals. DNA sequencing of the aberrant bands demonstrated a G to A substitution in all affected patients; this point mutation results in the substitution of a highly conserved valine residue with a methionine (V822M) in the cyclic nucleotide-binding domain of this potassium channel. The cosegregation of this distinct mutation with LQT demonstrates that *HERG* is the LQT gene in this pedigree. Furthermore, the location and character of this mutation suggests that the cyclic nucleotide-binding domain of the potassium channel encoded by *HERG* plays an important role in normal cardiac repolarization and may decrease susceptibility to ventricular tachyarrhythmias.

KEY WORDS: long QT syndrome, linkage, arrhythmias, missense mutation, cyclic nucleotide-binding domain, potassium channel

INTRODUCTION

Familial long QT syndrome (LQT) is a rare disorder, predisposing children and adolescents to sudden death from ventricular tachyarrhythmias. Since the initial report of the disease more than a century ago, two inherited forms of LQT have been described: Jervell and Lange-Nielsen syndrome, an autosomal-recessive disease associated with congenital neural deafness, and the more common autosomal-dominant familial form, Romano-Ward syndrome, which is not associated with deafness [Jackman et al., 1988; Jervell and Lange-Nielsen, 1957; Romano et al., 1963; Ward, 1964]. In addition, sporadic and acquired forms of LQT have been reported [Schwartz, 1985; Zipes, 1987]. Drug-induced LQT is by far the most common acquired form, but LQT can also be caused by neurologic, metabolic, or other cardiac abnormalities. The LQT syndromes are characterized by a spectrum of symptoms including recurrent syncope, palpitations, and seizures [Schwartz, 1985]. The diagnosis of LQT is based on the presence of pathognomic electrocardiographic abnormalities such as an abnormal prolongation of the QT interval, for which the disease is named [Schwartz et al., 1995]. Repolarization abnormalities, such as T-wave alternans and asymmetric or notched T or U waves, are also observed. Clinical studies have demonstrated that the QT interval varies according to gender, age, heart rate, and autonomic tone, only adding to the complexity of accurate diagnoses [Schwartz et al., 1995]. Recent studies have focused on deciphering the molecular genetic basis of the potentially fatal cardiac arrhythmias.

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Address reprint requests to Carol Ann Satler, M.D., Ph.D., Department of Cardiology, Children's Hospital, 300 Longwood Avenue-Enders 13, Boston, MA 02115.

Genetic linkage investigations first mapped the *LQT1* locus to 11p15.5 in seven families, and the disease was thought to be homogeneous [Keating et al., 1991a,b]. However, further studies of affected families localized the disease phenotype to several other loci, demonstrating heterogeneity: *LQT2* on 7q35–36, *LQT3* on 3p21–24, and *LQT4* on 4q25–27 [Benhorin et al., 1993; Curran et al., 1993; Jiang et al., 1994; Schott et al., 1995; Towbin et al., 1994]. Recently, mutations associated with LQT were identified in a putative cardiac potassium channel gene, *HERG*, on chromosome arm 7q; in a cardiac sodium channel gene, *SCN5A*, on chromosome arm 3p; and in a putative cardiac potassium channel gene, *KVLQT1*, on chromosome arm 11p [Curran et al., 1995; Wang et al., 1995a, 1996]. These findings support the hypothesis that the cardiac arrhythmias associated with LQT may result from mutations in cardiac-specific ion channel genes or in genes that regulate cardiac ion channels [Keating, 1995]. The clinical variability of LQT, within and among families, may be due to genetic heterogeneity.

In this study, we identified a novel mutation associated with LQT in a previously unreported, multigenerational LQT family of Irish descent. Clinical and genetic analyses were performed to show linkage of LQT in this family to *LQT2* on 7q. Additional genetic analysis identified a missense mutation within the cyclic nucleotide-binding domain of the potassium channel gene encoding *HERG*. The location and character of this mutation suggests that the cyclic nucleotide-binding domain of *HERG* plays an important role in cardiac repolarization.

MATERIALS AND METHODS

Clinical Evaluations

A large Irish family followed at the Cardiology Service at Children's Hospital, Boston, was selected for further evaluation. Informed consent was obtained prior to enrollment from all participants in accordance with the Children's Hospital Committee of Clinical Investigation. All relatives were evaluated by family history, physical examination, and 12-lead electrocardiography. Electrocardiograms were interpreted according to standard criteria, and measurement of the corrected QT interval, QTc, was determined using established methods [Bazett, 1920]. The diagnosis of long QT syndrome was made according to a modified diagnostic criteria system previously reported, and was made without knowledge of DNA patterns [Schwartz, 1985; Schwartz et al., 1993]. This system assigns relative points to various electrocardiographic, clinical, and familial findings. We modified this system to include prominent U waves in the electrocardiographic findings and palpitations in the clinical history. Scores range from 0–10.5 points. Diagnosis of LQT was made on the basis of a total score $\geq$4.5 points. Because accurate phenotypic characterization is critical, individuals who had a score of 2.5–4.0 points were assigned "indeterminate" phenotypes during linkage analysis. The results of phenotypic analyses were in accord with previously established methods [Keating et al., 1991a]. Congenital deafness was not observed. Also, the relatives evaluated had no history of neurologic and metabolic abnormalities or documented use of drugs or medications known to prolong the QT interval.

Genotypic Analyses

For genotypic analyses, 5–10 ml of peripheral blood were obtained from each relative. Genomic DNA was isolated from lymphocytes by standard methods [Moore, 1994]. Polymorphic short tandem-repeat sequences (also termed microsatellites) were amplified with the polymerase chain reaction (PCR) using published nucleotide primer sequences [Buetow et al., 1994; Gyapay et al., 1994]. Radiolabeled PCR reactions were performed, and products were resolved on polyacrylamide gels and visualized following autoradiography, as previously described [Jacob et al., 1995]. In brief, genomic DNA (5 μl; 4 ng μl^{-1}) was amplified in a volume of 10 μl containing 120 nM of unlabeled oligonucleotide primer and 120 nM of primer end-labeled with ^{32}P; 200 μM each of deoxyadenosine triphosphate, deoxycytidine triphosphate, deoxyguanosine triphosphate, and deoxythymidine triphosphate; and 0.3U of *Taq* DNA polymerase (Boehringer Mannheim, Indianapolis, IN) with 1 $\times$ PCR buffer (10 mM TRIS, pH 8.3.; 50 mM potassium chloride; and 0.15 mM magnesium chloride) (Boehringer Mannheim). The samples were processed using the following thermocycler protocol: initial denaturation for 3 min at 92°C, followed by 25 cycles, including denaturation for 1 min at 92°C, primer annealing for 2 min at 55°C, and primer extension for 1.5 min at 72°C; at the end of the last cycle there were 7 min of extension at 72°C. The amplified products were diluted with 10 μl 95% formamide dye electrophoresed on 6% polyacrylamide sequencing gels and visualized by autoradiography.

Linkage Analysis

To determine whether the DNA markers cosegregated with the locus for familial long QT syndrome, two-point analyses were performed with MLINK (version 5.10), and multipoint analyses were performed with the FASTLINK version of LINKMAP [Cottingham et al., 1993; Lathrop et al., 1984; Schaffer et al., 1994]. Two individuals analyzed the data, independently and without knowledge of each relative's disease status, to determine the genomic alleles present in each individual. There was complete agreement in the assignment of alleles between reviewers. Penetrance of LQT was set at 90%, and disease gene frequency was assumed to be 0.001 and equal between males and females. Allele frequencies were taken from published data when available, and were otherwise determined independently in the population studied and used in linkage calculations as described previously [Jiang et al., 1994].

SSCP Analyses and DNA Sequence Analysis

Genomic DNA samples were amplified by PCR as described above and used in single-strand conformation polymorphism (SSCP) analyses [Orita et al., 1989; Ptacek et al., 1991]. The primer pairs *HERG 3–9* and *HERG 5–11* used in this study were previously described [Curran et al., 1995]. Annealing temperature

was 58°C for these PCRs. An additional primer pair *HERG* 30–31 was designed based on published cDNA sequences and intronic sequences and spanned a portion of the cyclic nucleotide-binding domain of *HERG* [Curran et al., 1995; Warmke and Ganetzky, 1993]. The nucleotide sequence of these primers were *HERG*-30: 5′-CCGGGAGAAGGTGCCTGCTGCCTGGA-3′ (forward primer), and *HERG*-31: 5′-TGGTCGGAGAACTCAGGGTACATGTC-3′ (reverse primer). Annealing temperature was 65°C for these PCRs. Amplified radiolabeled PCR products were diluted twofold with 95% formamide dye, denatured by heating at 95°C for 5 min, then placed on ice for 5 min, and 3 μl of each sample were electrophoresed on 7.5% nondenaturing polyacrylamide gels (49:1 polyacrylamide: bisacrylamide) at 4°C. Electrophoresis was performed at 40 W for 2–5 hr. Gels were transferred to filter paper, dried, and exposed to X-ray film at −80°C for 12–36 hr.

Normal and aberrant SSCP conformers were cut directly from dried gels and eluted in 100 μl of distilled water at 25°C for 2 hr. The eluted DNA (5 μl) was used as a template for a second PCR using the original primer pair. Amplified products were purified through 1.5% low-melting agarose. These products were sequenced directly on the Applied Biosystems model 373A DNA sequencer (Applied BioSystems, Foster City, CA).

RESULTS

Clinical Analyses

To identify a DNA marker linked to the gene responsible for long QT syndrome, 48 members of a large Irish kindred (n = 120) were evaluated clinically (Fig. 1). Of 48 relatives in four generations at risk for inheriting this disorder, 16 relatives (6 male and 10 female) were affected: a pattern suggestive of autosomal-dominant inheritance. Clinical evaluations or examinations of historical records demonstrated that affected relatives were the parents or offspring of affected individuals, indicating a high penetrance of the disease gene. The manifestations of the affected relatives are shown in Table I. Seven affected relatives, based on electrocardiographic findings, were asymptomatic, whereas one had undergone a left cardiac sympathectomy for refractory symptoms. A history of palpitations was documented in 3 affected relatives, and syncopal events were noted in 7 individuals. Seizures were reported by 2 affected relatives. In addition, 2 individuals experienced "aborted" sudden cardiac death. Although affected, individual IV-23 had a normal QTc interval; other findings of her electrocardiogram and her clinical history were diagnostic of long QT syndrome.

Seventeen relatives did not have clinical or electrocardiographic abnormalities of long QT syndrome. Fifteen individuals had an "indeterminate" phenotype according to the diagnostic criteria system previously described.

Genetic Analyses

Highly polymorphic short tandem-repeat sequences dispersed throughout the genome were analyzed for linkage to the long QT syndrome locus in this kindred [Buetow et al., 1994; Gyapay et al., 1994]. Because previous reports had described linkage of the disease gene to chromosomes 3, 4, and 11 in patients with the syndrome, markers from these regions were selected for initial analyses [Jiang et al., 1994; Keating et al., 1991a,b; Schott et al., 1995]. Linkage to these genomic regions was excluded (calculated lod scores, <-2.0; data not shown). Approximately 70% of the human genome was excluded before linkage was detected between marker *D7S483*, on 7q, and the long QT syndrome locus (lod scores, >3.0; $\theta = 0.067$). Long QT syndrome was recently mapped to 7q in nine families [Jiang et al., 1994]. Additional short tandem-repeat markers (*D7S676, D7S688, D7S505, D7S636*, and *D7S798*) in this region were tested. The maximal two-point lod score achieved with marker *D7S636* was 6.93 ($\theta = 0.00$) (Table II), providing odds of more than 8,500,000:1 that the gene responsible for long QT syndrome in this kindred is located on 7q. The genotypes of 2 clearly affected relatives (subjects III-6 and IV-18) suggest that a recombination event had occurred between locus *D7S688* and the long QT syndrome gene. Analyses also identified recombination between *D7S483* and the disease gene in subject II-1. Collectively, these data mapped the gene responsible for long QT syndrome to a region between *D7S688–D7S483* (Fig. 2).

HERG previously mapped to the region between *D7S505–D7S483* on chromosome 7q35–36 using two physical mapping techniques: yeast artificial chromosome (YAC) contigs constructed for chromosome 7, and fluorescent in situ hybridization (FISH) with a P1 clone containing *HERG* [Curran et al., 1995]. In nine previously reported LQT families, *HERG* was linked genetically to the LQT locus [Curran et al., 1995]. Using single-strand conformation polymorphism (SSCP) analyses to identify previously described polymorphisms within *HERG*, we performed linkage analyses in this chromosome 7q-linked kindred. Two aberrant SSCP conformers were identified in DNA samples from patients with the polymorphic *HERG* primer pairs *5–11* (observed heterozygosity of 0.37) and *3–9* (observed heterozygosity of 0.44). *HERG* polymorphisms were used for genotypic analyses in this kindred, as previously described (Fig. 1). No recombinant events between *HERG* and LQT were identified in this family. The maximum lod score for this family was 2.11 with *HERG* primer pairs *5–11* ($\theta = 0.00$; Table II). Although the polymorphism information content of these *HERG* markers is low, these data demonstrate that *HERG* is linked to LQT in this family. Further linkage analysis excluded two candidate genes, a chloride channel gene *CLCN1* and a muscarinic-acetylcholine receptor gene *CHRM2*, which map to this region (data not shown).

Multipoint analysis was used to determine linkage of the disease phenotype to a set of marker loci whose relative locations are known. The results confirm the two-point data, and the multipoint Z values shown in Figure 3 reach their maximum between markers *D7S505–D7S636*.

SSCP Analyses and DNA Sequence Analysis

To test the hypothesis that *HERG* is the gene responsible for LQT in this kindred, we used SSCP analyses to

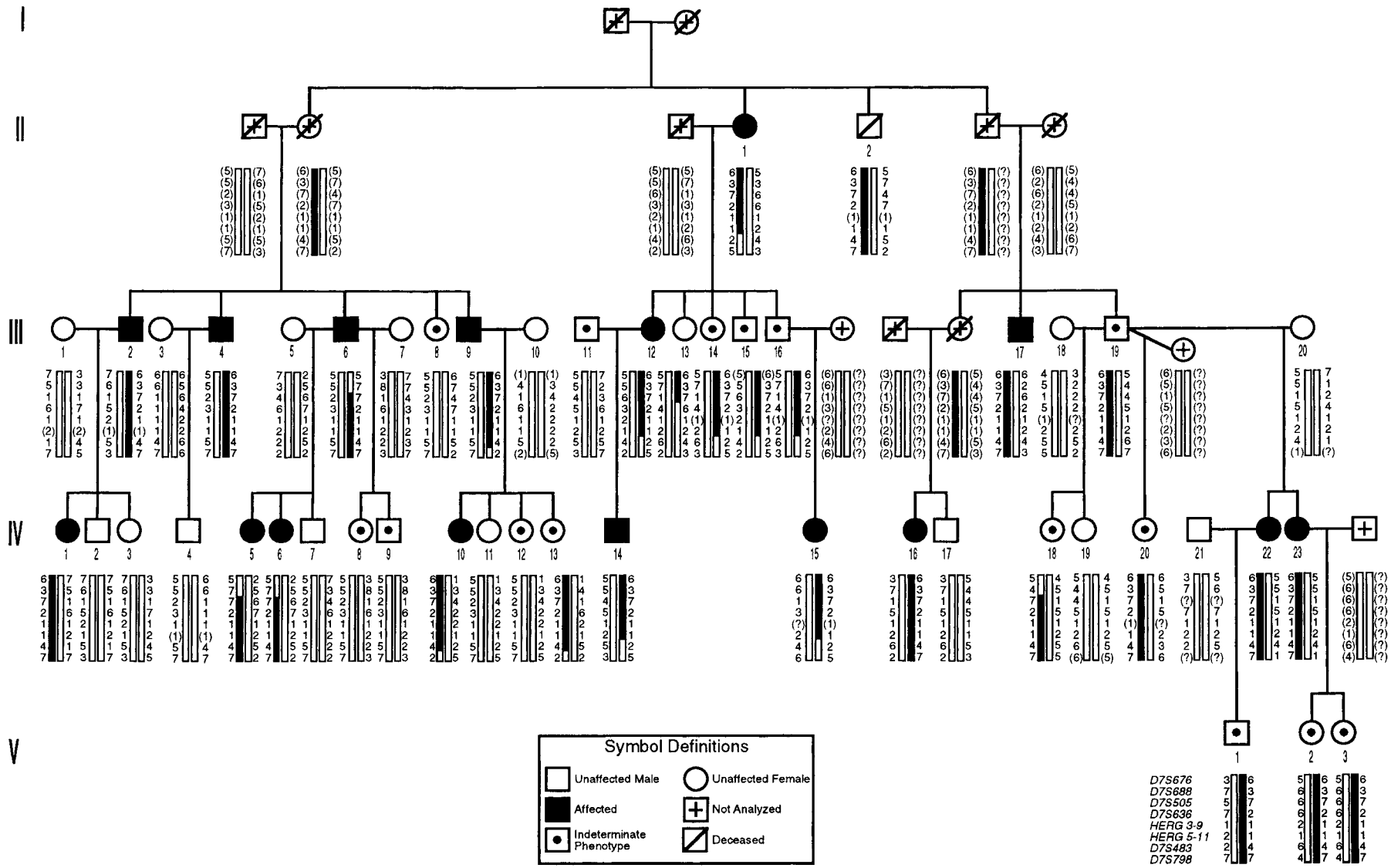

Fig. 1. Genotypic data for 7q polymorphic microsatellite markers, listed in centromere-to-telomere order, are shown for an LQT kindred. PCR typings are grouped in most likely paternal and maternal haplotypes. Genotypes indicated in parentheses are inferred from genotypes of their children. Alleles from the original nonrecombinant chromosome haplotype that cosegregated with the disease gene are marked by a solid bar. The individual's identification number is shown below his or her pedigree symbol.

TABLE I. Clinical Symptoms of Affected Relatives*

Subject no.	Age/sex	QT^c	Palpitations	Syncope	Seizures	Aborted sudden death
II-1	84/F	0.49	–	–	–	–
III-2	55/M	0.63	+	–	–	–
III-4	61/M	0.64	–	+	–	–
III-6	53/M	0.48	–	–	–	–
III-9	52/M	0.60	–	–	–	–
III-12	50/F	0.50	–	+	–	–
III-17	48/M	0.50	–	+	–	–
IV-1	28/F	0.60	–	–	–	–
IV-5	16/F	0.60	–	+	–	–
IV-6	18/F	0.55	–	+	–	–
IV-10	20/F	0.61	–	–	–	–
IV-14	23/M	0.55	–	–	+	–
IV-15	20/F	0.53	–	–	–	–
IV-16	35/F	0.63	+	+	–	+
IV-22	31/F	0.54	–	–	–	–
IV-23	32/F	0.44	+	+	+	+

* QT_c, corrected QT interval, defined in Bazett [1920] and cited in Materials and Methods.

screen for mutations in affected individuals. SSCP using the primer pair *HERG 30–31* spanning the cyclic nucleotide-binding domain of *HERG* identified the aberrant conformer in affected individuals of LQTS001 (Fig. 4). Analysis of more than 65 unaffected individuals failed to show this anomaly. The normal and aberrant conformers were sequenced, revealing a G to A substitution at position 2647 (Fig. 5). This mutation results in a substitution of a methionine for a highly conserved valine at codon 822 (V822M), altering the cyclic nucleotide-binding domain of the *HERG* protein (Fig. 6).

DISCUSSION

Gene mapping and subsequent mutational analyses are important steps toward the complete identification and characterization of long QT gene(s). Through genetic analysis, we obtained data that provide strong support for linkage of LQT to 7q in this family, and we localized the disease gene for LQT within a ~1.8-cM region flanked by markers *D7S505* and *D7S636*. A putative cardiac potassium channel gene, *HERG*, previously mapped to this region. Using single-strand conformational polymorphism analyses, we identified a novel missense mutation within the cyclic nucleotide-binding domain (NBD) of the potassium channel encoded by *HERG*. Our findings not only suggest that *HERG* is the LQT gene in this pedigree, but that the cyclic nucleotide-binding domain of this channel plays a significant role in normal cardiac repolarization.

The cardiac arrhythmias associated with LQT probably result from mutations in cardiac-specific ion channel genes or in genes that regulate their function [Keating, 1995]. Seven *HERG* mutations have previously been identified in chromosome 7-linked LQT families [Benson et al., 1996; Curran et al., 1995]. They include two intragenic deletions, one splice donor mutation, and four missense mutations (Fig. 7). Four of these mutations affect the membrane-spanning domains of the protein encoded by *HERG*, and two of these mutations affect the pore-forming region. In two mutations, the cyclic NBD is deleted. The missense mutation described in this paper is unique because it results in a substitution of a methionine for a highly conserved valine at codon 822 (V822M) within the NBD.

Additional mutations in a cardiac sodium channel, *SCN5A*, and in a putative cardiac potassium channel, *KVLQT1*, have also been reported for other LQT families. These families have been linked to chromosomes 3 and 11, respectively [Wang et al., 1995a, b, 1996]. Distinct mutations within one LQT gene or different LQT genes could account for the diverse clinical findings found in LQT families.

TABLE II. Pairwise lod Scores Between Chromosome 7q Markers and LQT

	Z at recombination fraction (θ)								
Locus	0.00	0.01	0.05	0.10	0.20	0.30	0.40	Z_{max}	$\hat{\theta}$
D7S676	−0.96	2.32	2.73	2.64	2.05	1.24	0.45	2.74	0.057
D7S688	0.62	3.68	4.02	3.85	3.15	2.23	1.19	4.02	0.047
D7S505	5.82	5.77	5.52	5.11	4.08	2.82	1.37	5.82	0.000
D7S636	6.93	6.83	6.41	5.85	4.59	3.16	1.55	6.93	0.000
HERG 3–9	1.33	1.31	1.20	1.06	0.78	0.51	0.25	1.33	0.000
HERG 5–11	2.11	2.06	1.86	1.60	1.09	0.63	0.24	2.11	0.000
D7S483	0.77	2.63	3.15	3.11	2.57	1.75	0.82	3.17	0.067
D7S798	−5.89	−0.25	1.02	1.36	1.27	0.83	0.32	1.40	0.129

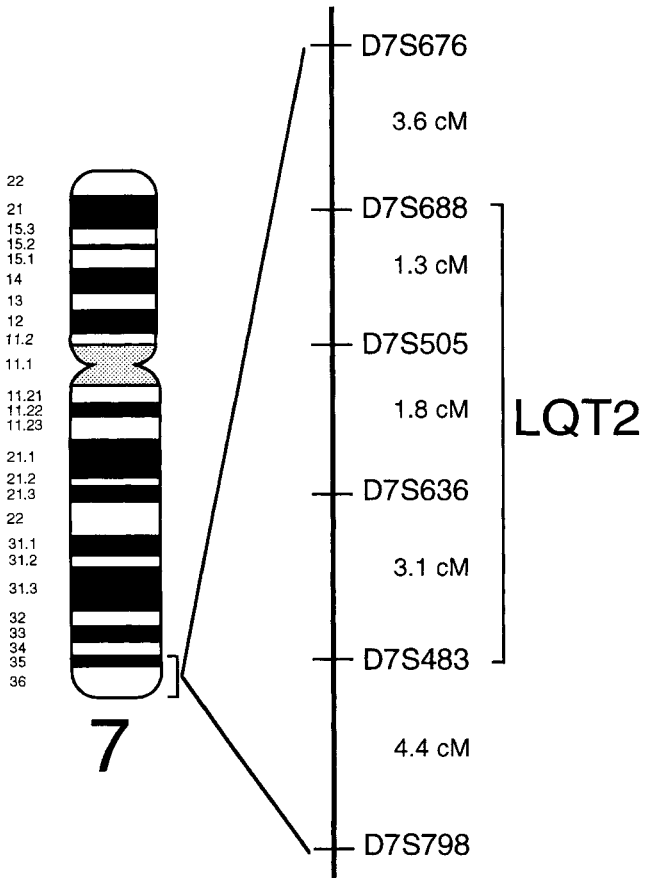

Fig. 2. Ideogram of chromosome 7, illustrating the location of the LQT gene for this family, with defined flanking markers and other polymorphic loci in the 7q region. The genetic distance between markers is shown in centimorgans [Buetow et al., 1994; Gyapay et al., 1994]. On the basis of genetic and physical maps of the location of flanking markers, the LQT gene should lie in the 7q35–36 region.

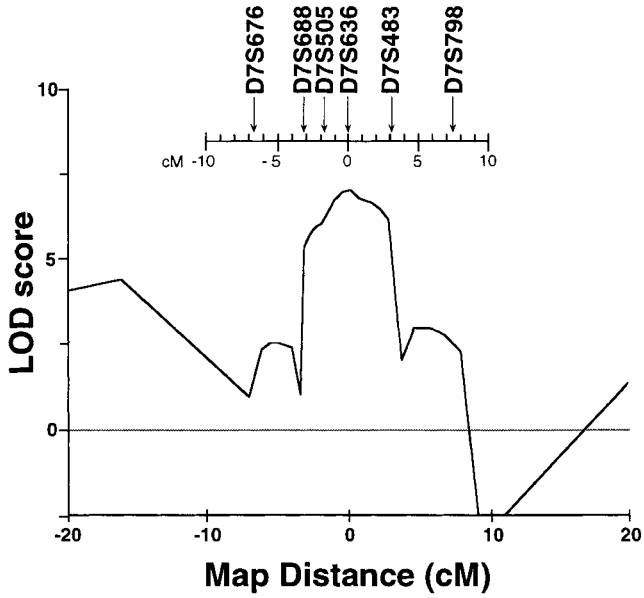

Fig. 3. Multipoint linkage map generated with the FASTLINK version of LINKMAP using chromosome 7q markers [Cottingham et al., 1993; Schaffer et al., 1994]. The order and genetic distance of the markers used in the analyses are shown [Buetow et al., 1994; Gyapay et al., 1994]. The highest likelihood for location of the LQT gene for this family is between loci defined by markers *D7S505* and *D7S636*.

It was originally suggested that the pathogenesis of LQT involves either a defect in myocellular repolarization or predominance of left autonomic innervation [Jackman et al., 1988; Schwartz et al., 1995]. The prolonged QT interval on the electrocardiograms of affected individuals has been attributed to abnormally slow repolarization of ventricular action potentials or to the presence of afterdepolarizations [Jackman et al., 1988; Trudeau et al., 1995]. Since potassium currents play a significant role in the plateau and repolarization phases of the cardiac action potential, genes involved with the structure and function of cardiac potassium channels are likely candidates for LQT. Genetic linkage and subsequent mutational analyses have since corroborated this hypothesis, favoring abnormalities in myocellular repolarization [Curran et al., 1995].

Recent studies have shown that *HERG* encodes an inwardly rectifying potassium channel gene that prolongs potassium efflux during repolarization [Sanguinetti et al., 1995; Trudeau et al., 1995]. It has been proposed that *HERG* also encodes a component of I_{kr}, the rapidly activating delayed rectifier K^+ current in cardiac myocytes, which contributes significantly to the repolarization of the action potential. Recent studies suggest that electrophysiologic characteristics of this channel play a specific role in the normal suppression of arrhythmias [Smith et al., 1996]. A complete characterization of LQT genes and their genetic defects may not only help explain the electrophysiology and pathology of this disease, but allow for the development of new and highly specified treatments.

The spectrum of *HERG* channel dysfunction in LQT is unknown. The heterologous expression of mutant

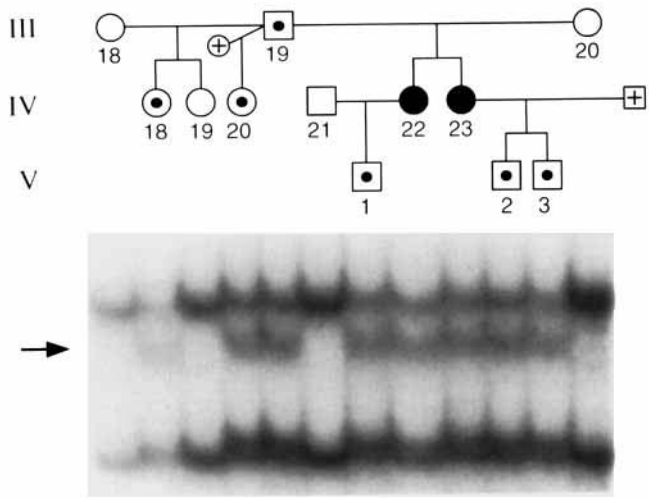

Fig. 4. Subset pedigree structure of LQTS001 is shown. Below pedigree, results of SSCP analyses with primer pair *HERG 30–31* are shown. Aberrant SSCP conformers cosegregate with the disease in this kindred.

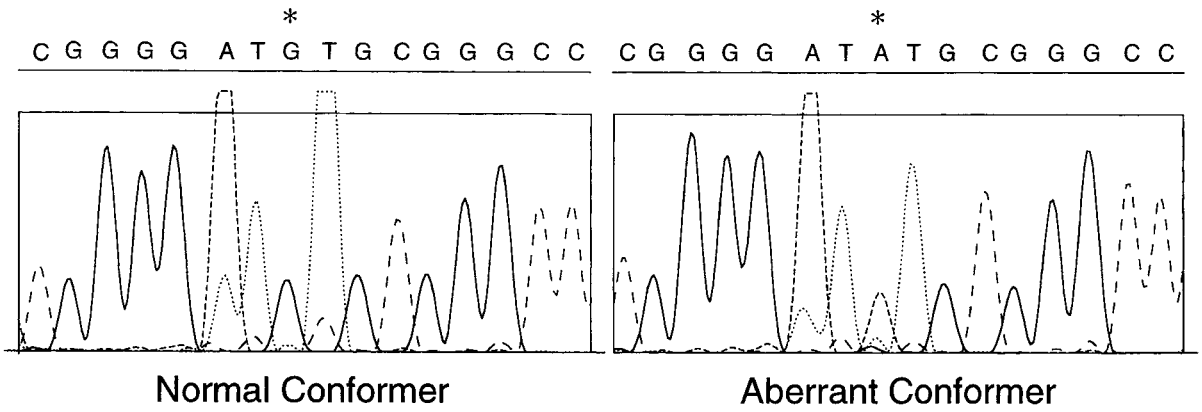

Fig. 5. DNA sequence analyses of normal and aberrant SSCP conformers, as shown in Figure 4, demonstrates a G to A substitution at position 2647. This mutation results in a substitution of methionine for a highly conserved valine residue in the cyclic nucleotide-binding domain of *HERG*.

and wild-type *HERG* complementary RNA in *Xenopus* oocytes has been used to define the mechanism of LQT [Sanguinetti et al., 1996]. Some mutations cause dominant negative suppression of *HERG* function, whereas other mutations cause a complete loss of function. It has been hypothesized that these mutations diminish I_{kr} and delay ventricular repolarization, as observed in affected individuals with a prolonged QT interval. It has been speculated that *HERG* channel function may be modulated by second messenger cyclic nucleotides [Sanguinetti et al., 1995]. Changes in cyclic nucleotide concentration may be involved in regulating membrane excitability and may suggest a mechanism for the link between altered autonomic nervous activity and arrhythmias in LQT [Curran et al., 1995]. Even though *HERG* current is not affected by cyclic nucleotides when *HERG* is expressed in *Xenopus* oocytes, the electrophysiological properties of *HERG* in vivo may be different [Sanguinetti et al., 1995]. *Drosophila eag* encodes a channel which is structurally related to voltage-activated K^+ channels and cyclic nucleotide-gated cation channels, and to *HERG* (approximately 50% sequence homology) [Warmke and Ganetzky, 1993]. Experiments evaluating the electrophysiological properties of *eag* have shown that it is permeable to K^+ and Ca^{2+} and modulated by cAMP [Brüggemann et al., 1993]. Future studies should examine modulation of *HERG* function in more detail, including the electrophysiological effects of the LQT-associated missense mutation in the nucleotide-binding domain of the potassium channel encoded by *HERG*.

To date we have studied 30 unrelated families with LQT. It is likely that 50% of families are similarly linked to 7q35–q36 [Curran et al., 1995]. However, we observed significant differences in clinical symptomatology between the family in this study and other LQT families similarly linked to chromosome 7q. This finding suggests that different mutations in a single ge-

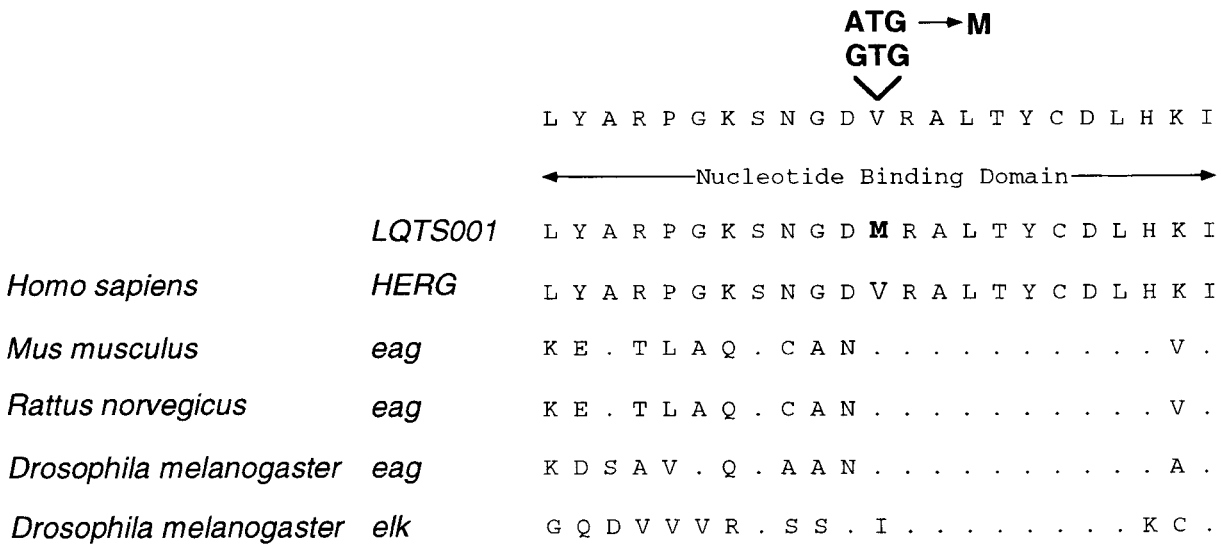

Fig. 6. Amino-acid sequence alignment of the cyclic nucleotide-binding domain of the *eag* family of potassium channels from various species. Note the highly conserved valine at codon 822. The mutation in pedigree LQTS001 results in substitution of methionine for this valine. All sequences were obtained from the Genome Data Bank.

netic locus on chromosome 7q or different modifiers in the genome are responsible for LQT in our unrelated families. Significant variability in clinical symptomatology is also observed within this family. The severity of the disease was greater in 2 individuals, IV-16 and IV-23, who not only experienced syncopal events, but "aborted" sudden death (Table I). It is likely that the phenotypic expression of the disease gene is influenced by modifier genes, physiological factors, or environmental differences that play a regulatory role in gene expression. To date, the HLA-DR locus is the only modifier locus that has been demonstrated to have a significant effect on the clinical expression of the LQT phenotype [Weitkamp et al., 1994].

Further analyses of phenotype/genotype correlations among LQT families have important implications for management and treatment of affected members. Since treatment for LQT exists, identification of LQT genes and LQT gene mutations will lead to improvements in the diagnostic and therapeutic modalities available to LQT families from presymptomatic to symptomatic stages. Already, identification of the disease-causing mutation has enabled presymptomatic genetic diagnoses in this 7q-linked family. A complete characterization of LQT genes may not only benefit all LQT families at risk for sudden death due to tachyarrhythmias, but may also elucidate a common physiological mechanism of arrhythmias in this and other cardiovascular diseases.

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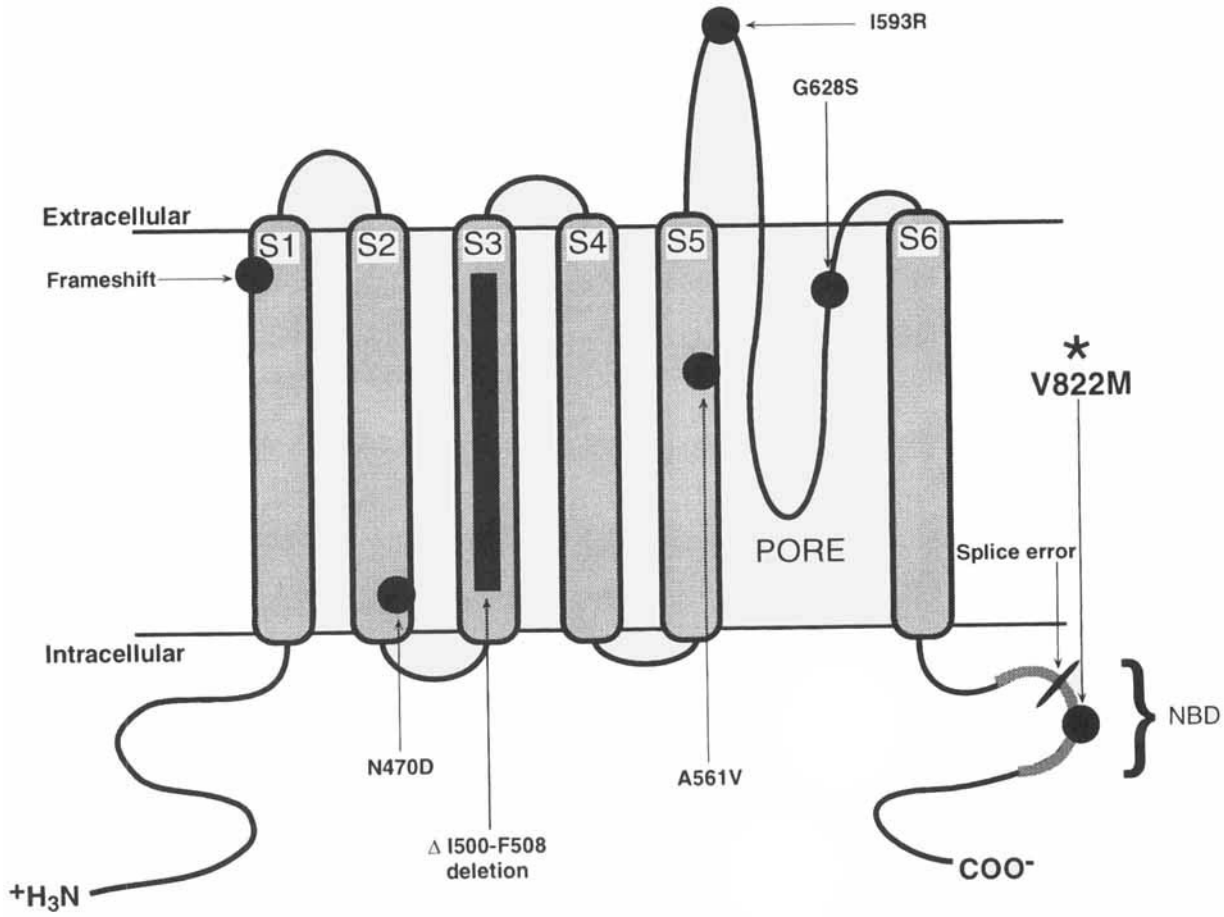

Fig. 7. Putative transmembrane topology of protein encoded by *HERG* and the location of known LQT-associated mutations [Curran et al., 1995; Benson et al., 1996]. This channel has six putative transmembrane segments (S1–S6), a loop between segments S5–S6 that dips into the membrane to form part of the pore, and a cyclic nucleotide-binding domain (NBD). The mutation in pedigree LQTS001 in the NBD is indicated by an asterisk.

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